gested for lotusin, are, like lotusin, easily decomposed by dilute hydrochloric acid, forming prussic acid and the corresponding aldehyde or ketone.

The authors wish again to express their obligations to Mr. Ernest A. Floyer, of Cairo, Member of the Egyptian Institute, who has spared neither trouble nor expense in collecting in Egypt, and despatching to this country, the material required for this investigation.

"The Pharmacology of Pseudaconitine and Japaconitine considered in relation to that of Aconitine." By J. Theodore Cash, M.D., F.R.S., Regius Professor of Materia Medica in the University of Aberdeen, and Wyndham R. Dunstan, M.A., F.R.S., Director of the Scientific Department of the Imperial Institute. Received June 11—Read June 20, 1901.

(Abstract.)

In a previous paper on the Pharmacology of Aconitine and some of its principal derivatives,* we have given an account of the physiological action of this, the highly toxic alkaloid of Monkshood (*Aconitum Napellus*), and of its principal derivatives, and we have also discussed the ascertained physiological effects of these substances in relation to their chemical constitution. The results of this investigation have proved to be of much practical importance in connection with the pharmaceutical and medical employment of aconite, especially in demonstrating the partial antagonism to aconitine of benzaconine, and in a greater degree of aconine, both of which derivatives accompany the parent alkaloid in the plant and in the pharmaceutical preparations made from it, which have been hitherto used medicinally. Although it seems likely that these separate alkaloids, and especially aconine, may be useful as therapeutic agents, it is now clear that for the purpose for which aconite is employed, the pure alkaloid, aconitine, should be used in the place of the indefinite mixture of physiologically antagonistic alkaloids contained in pharmaceutical preparations made from the plant.

In a series of papers communicated to the Chemical Society, and published in the 'Journal of the Chemical Society' (1891–99), one of us, in conjunction with his pupils, has described the chemical properties of the toxic alkaloid contained in two other species of alkaloid, viz., *Aconitum ferox* or Indian or Nepaul Aconite, and *Aconitum Fischeri* or Japanese Aconite. The medicinal employment of these potent drugs

* 'Phil. Trans.,' B, 1898, vol. 190, p. 239.

has been very restricted in the absence of any definite knowledge as to the nature of their constituents and the physiological action to which they give rise.

Aconitum ferox has long been known to botanists and travellers in India as a poisonous plant of great virulence. It is used in Indian medical practice under the vernacular name of "Bikh." There appear however to be several varieties of aconite passing under this vernacular name. This is a subject which we are at present investigating with the assistance of the Government of India.

In 1878 Alder Wright isolated a crystalline, highly toxic alkaloid, from the root of the plant, and named it pseudaconitine. In 1897* one of us gave an account of a complete investigation of the chemistry of this alkaloid, the results of which have led to a modification in certain important respects of the conclusions arrived at by Wright and his co-workers. Our results have been confirmed by Freund and Niederhofheim.†

For details of the chemistry of pseudaconitine and its derivatives, reference must be made to the paper already referred to.‡ We may here briefly record the chief properties of the alkaloid.

Pseudaconitine is a crystalline alkaloid whose composition differs from that of aconitine, being expressed by the formula $C_{36}H_{49}NO_{12}$. The crystals melt at 202°, and are sparingly soluble in water, but readily in alcohol. The salts are usually crystalline and soluble in water. Their solution and those of the base produce, in excessively minute quantities, a persistent tingling of the tongue, lips, and other surfaces with which they are placed in contact, in this respect resembling aconitine and its salts, which produce the same effect.

When heated in the dry state at its melting point pseudaconitine evolves a molecular proportion of acetic acid, leaving another alkaloid, pyropseudaconitine. This alkaloid, like the corresponding pyro-derivative of aconitine, does not give rise to the characteristic tingling effects of the parent base.

When a salt of pseudaconitine is heated in a closed tube with water, as in the case of aconitine, partial hydrolysis occurs with the loss of a molecule of acetic acid, an alkaloid, veratryl-pseudaconine, being left. This alkaloid, like the corresponding benzaconine, derived by similar means from aconitine, produces neither the tingling sensation nor the toxic effects of the parent base.

The complete hydrolysis of pseudaconitine, which is reached when the above-mentioned veratryl-pseudaconine is heated with alkalis, produces, instead of the benzoic acid furnished by aconitine, veratric or dimethylprotocatechuic acid, together with a base, pseudaconine, not

* 'Proc. Chem. Soc.,' 1895, p. 154; 'Trans. Chem. Soc.,' 1897, p. 350.

† 'Ber.,' vol. 29, pp. 6, 852.

‡ *Loc. cit.*

susceptible of further hydrolysis. Whilst there is thus a strong general resemblance in chemical constitution between pseudaconitine and aconitine, the benzoic radical of aconitine is replaced in pseudaconitine by the veratric radical of veratric acid, whilst there are probably also constitutional differences in the central nucleus.

The composition and properties of the toxic alkaloid present in Japanese aconite, "Kuza-uzu," regarded by botanists as *Aconitum japonicum* or *A. Fischeri*, has been the subject of some dispute among chemists who have examined it. Wright regarded it as chemically different from aconitine, both in composition and in structure, being an anhydro- or apo-derivative formed by the loss of water and conjugation of 2 molecules of an unknown alkaloid of the aconitine type. He assigned to it the formula $C_{66}H_{88}N_2O_{21}$. Lübbe afterwards studied the properties of japaconitine, and pronounced it to be identical with aconitine, and, more recently, Freund and Beck have reached the same conclusion. Later, one of us, in conjunction with H. M. Read,* subjected japaconitine to a very detailed investigation, in the course of which its properties and those of its principal derivatives were defined and compared closely with those of aconitine. We believe that these results leave little room for doubting that japaconitine is a distinct alkaloid different from aconitine, although Wright was mistaken in the view he took of its composition and constitution. Superficially japaconitine bears a very strong resemblance to aconitine; it is, however, richer in carbon, and the physical properties of its derivatives do not agree with those of aconitine. To this alkaloid we have provisionally assigned the formula $C_{34}H_{49}NO_{11}$, and have retained for it the name of japaconitine suggested by Wright.

In general, the decomposition of japaconitine resembles that of aconitine, but the physical properties of the resulting derivatives are not the same. By the action of heat it furnishes acetic acid and jappyraconitine; on partial hydrolysis, japbenzaconine is obtained besides acetic acid; whilst on complete hydrolysis, the products are acetic acid, benzoic acid, and japaconine. Whilst therefore the constitution of the central nucleus appears to be different, both aconitine and japaconitine contain the acetyl and benzoyl groups, whilst in pseudaconitine the acetyl and veratryl groups are present.

In the present paper the physiological action of specially purified pseudaconitine and japaconitine is recorded and compared with aconitine.

The differences found are nearly always differences of degree and not differences of kind, a result which bears out the close constitutional relationship which is to be inferred from their chemical reactions. Although there are probably constitutional differences in the central nuclei of the three alkaloids, the same constitutional type is to

* 'Journ. Chem. Soc.,' 1899.

be seen in each, and the substitution of a veratryl group (in pseudaconitine) for an acetyl group (in aconitine) counts for little in influencing the characteristic physiological action.

In order to bring the action of aconitine, pseudaconitine, and japaconitine into a contrast, which may be readily apprehended at a glance, the following summary will be useful.

Heart.—All three alkaloids have a similar effect upon the heart of such mammals as have been observed. Pseudaconitine is quantitatively more energetic than the other two, towards cats, but is certainly not nearly twice as toxic when artificial respiration is practised. Towards the frog's heart pseudaconitine is slightly less powerful than the other two, of which japaconitine is rather the more active.

Vagus Nerve and Inhibitory Mechanism in Heart.—Heart slowing from increased central vagus activity is produced by all these alkaloids, and similar results follow section and stimulation of the nerve at this and later stages of poisoning by one and all of them, both in mammals and frogs.

Respiration.—There is less tendency to acceleration of respiration in mammals poisoned by pseudaconitine than when the other two alkaloids are employed; further, the dyspnœal conditions develop more suddenly and the central depression of respiration is greater. Japaconitine is at first slightly more depressant than aconitine, but thereafter the tendency to acceleration of respiration is sooner developed, otherwise the general features of their action are similar.

Blood.—All the aconitines produce a deleterious effect upon the hæmoglobin and coloured corpuscles of the blood when they are given repeatedly in large doses. As far as has been ascertained this is due to impairment in the nutrition of the animal rather than to a direct action.

Frogs kept in a watery medium or in contact with a moist surface develop œdema after receiving any of the aconitines, but this condition is most marked and the hydræmia of the blood is more pronounced and lasting after pseudaconitine.

Brain and Cord.—All aconitines appear to have a similar effect qualitatively on the brain and cord of rabbits, pigeons, and frogs.

Temperature.—The initial elevation of temperature often seen in rabbits which have received aconitine or japaconitine is less frequently observed after pseudaconitine. A slightly greater and more enduring fall of internal temperature is witnessed after the latter, when the dose is large and bears a like relationship to the lethal amount.

Repeated Administration.—Some tolerance is established on the part of rabbits towards all the aconitines, and this is manifested with reference to temperature reduction, to the cardiac effect, and, to a lesser extent, to respiration; the general toxicity undergoing a reduction which is not, however, extensive. Less tolerance is shown

towards pseudaconitine than towards the other two: it has been found impossible hitherto to determine how far rapidity of elimination varies between the alkaloids.

Sensory Nerves.—Local applications of the aconitine ointments of equal strengths are followed by a somewhat more powerfully depressant and enduring effect when these contain aconitine or japaconitine than pseudaconitine. This statement has reference to cutaneous sensory and thermic impressions in the human subject. The difference is at most but slight.

Motor Nerve and Muscle.—The action of the individual alkaloids is much the same whether specimens of *R. esculenta* or *R. temporaria* are used. It is more difficult to reduce reaction or to produce insensitiveness of the intramuscular motor nerves by pseudaconitine than by the other alkaloids. The so-called curare-like action has been found for all the alkaloids to be much feebler than was at one time supposed.

Direct contact of the alkaloidal solutions with muscle-nerve preparations reduces excitability, the muscle being affected by solutions containing less than 1 in 1,000,000, and the nerve by solutions still weaker. Pseudaconitine is recognised as producing a rather weaker effect than the two other alkaloids, which are nearly equal to one another, japaconitine being slightly the more energetic.

The results of the experiments detailed in this paper do not in all respects agree with previous observations; especially is this the case with regard to the relative toxicities of the three aconitines. The general order of toxicity towards mammals is pseudaconitine, japaconitine, and aconitine, which is the least toxic. Pseudaconitine has been found (roughly speaking) twice as toxic as aconitine towards the small mammals and birds used in the research. This agrees closely with the results of Adelheim* and Böhm and Ewers.† Cloetta‡ states that pseudaconitine is the stronger alkaloid, but gives no proportion. Our results differ from those of Nothnagel and Rossbach,§ who state that pseudaconitine is seventeen times as active as aconitine, and of Harnack and Meunicke,‖ who find the under margin of active dosage equal. Kobert¶ finds pseudaconitine and aconitine to be in activity "ziemlich gleich."

The relative toxicity of japaconitine to aconitine is approximately as ten to about nine towards the small mammals and birds which were used. Previously japaconitine has been seldom contrasted with the

* Adelheim, 'Forens. Chem. Untersuch,' Dorpat, 1860.

† Böhm and Ewers, 'Arch. f. Exp. Path. u. Pharm.,' 1873, Bd. 1, p. 385.

‡ Cloetta, 'Lehbr. d. Arzneim. u. Arzneiverordnungsl.' Freib., 1885.

§ Nothnagel u. Rossbach, 'Mat. Med. u. Therap.' (Fr.), 1880, 685.

‖ Harnack and Meunicke, 'Berl. Klin. Wchsch.,' 1883, No. 43, p. 657.

¶ Kobert, 'Lehbr. d. Intox.,' p. 657.

other two aconitines, but has been recognised as stronger than aconitine by Langaard,* and in one series of observations by Harnack and Meunicke. Kobert, on the other hand, does not separate japaconitine from aconitine and pseudaconitine in toxicity.

Dosage.—Based upon the observations made, the relative doses for therapeutical purposes would be approximately, regarding that for aconitine as the unit, for pseudaconitine 0·4 to 0·45, and for japaconitine 0·8.

Towards frogs the toxicity of these alkaloids is by no means so great (per gramme body-weight) as it is towards the same unit of the mammals and birds included in this research. Thus the lethal dose per kilo. mammalian weight may only be lethal to 140 to 170 grammes of frog weight, or even to less, according to the time of year. A medium-sized rabbit may therefore be poisoned by a dose of aconitine or japaconitine which would suffice to destroy six or eight frogs.

Japaconitine is slightly more toxic towards both mammals and frogs than is aconitine, but the higher toxicity of pseudaconitine towards birds and mammals is not associated with an equal activity towards frogs, for it exerts towards both *R. esculenta* and *R. temporaria* a slightly lower toxicity than do either of the other alkaloids.

There is no essential difference in the reaction of *R. esculenta* and *R. temporaria* respectively to individual aconitines beyond a greater or less accentuation of one or other symptom, as for example more excited movement in the latter, more reduction of reflex in the former, but in all parallel series of observations the resistance of *R. esculenta* has proved to be slightly greater to all the aconitines examined.

As concerns the local action of the aconitines upon sensory (cutaneous) structures in man, the differences are so trifling as to be negligible.

As regards the therapeutical employment of aconitine, japaconitine, and pseudaconitine, the great similarity in their physiological actions, amounting almost to a qualitative identity, which is established by this investigation, justifies the employment of any one for internal administration, provided that the dosage is properly regulated. Given in the proportions mentioned above, the three alkaloids would exert the same action. We strongly recommend the use of a pure alkaloidal salt in preference to preparations made from the plants, since the latter would be difficult to standardise, and even if this were done, the action of the aconitines would be modified to a greater or less extent by the other alkaloids present in the vegetable preparation.

For local applications the three alkaloids may be introduced into ointments in identical proportions. The greater toxicity of pseudaconitine need not prevent its use in this department of treatment if it

* Langaard, 'Arch. f. Path. Anat.,' 1880, 79, s. 229.

is remembered that all applications of the aconitines, externally, are to be considered dangerous if any abrasion of the skin is present.

The chemical part of this inquiry has been conducted in the Laboratories of the Scientific Department of the Imperial Institute, with the assistance and co-operation of the Government of India. Our thanks are specially due to Dr. George Watt, C.I.E., Reporter on Economic Products to the Government of India, for the interest he has shown in the investigation, and for the care he has taken in the collection of the necessary material.

The physiological experiments have been conducted in the Department of Materia Medica and Pharmacology of the University of Aberdeen, and have been assisted by a grant made by the Royal Society from the Government Fund. The assistance of Drs. Esslemont and Fraser has been very valuable in carrying out some of the observations entailed in this department of the research.

"The Pharmacology of Pyraconitine and Methylbenzaconine considered in Relation to their Chemical Constitution." By J. Theodore Cash, M.D., F.R.S., Regius Professor of Materia Medica in the University of Aberdeen, and Wyndham R. Dunstan, M.A., F.R.S., Director of the Scientific Department of the Imperial Institute. Received June 11,—Read June 20, 1901.

(Abstract.)

In a previous paper* we have shown that an entire change in the physiological action ensues on the withdrawal of the acetyl group from aconitine as is seen in the action of benzaconine, the first hydrolytic product of aconitine, from which it differs in containing an atom of hydrogen in the place of one acetyl group. This alkaloid is devoid of the characteristic physiological action and extraordinary toxicity of aconitine, whilst in respect of its action on the heart it is in the main antagonistic to that of the parent alkaloid. In order to study further the remarkable dependence of the physiological action on the presence of the acetyl group, we have examined the action of two derivatives of aconitine which we have obtained in this research, viz., pyraconitine and methylbenzaconine.

Pyraconitine was first prepared by one of us† by heating aconitine at its melting point, when the acetyl group is expelled as one molecule of acetic acid and the alkaloid pyraconitine remains. This compound

* 'Phil. Trans.,' B, 1898, vol. 190, p. 239.

† Dunstan and Carr, 'Trans. Chem. Soc.,' 1894, vol. 65, p. 176.